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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,479	12/08/2005	Brian Warner	2002P56020WOUS	7523

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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,479	WARNER ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on November 5, 2008 is acknowledged and has been entered. Claims 1-19 and 24-31 have been canceled. Claims 20-23 are pending.

Claims 20-23 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 5, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Previous Grounds of rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al. (US Patent 5,635,352; June 1997) in view of Erdogan et al. (Nucleic Acids Research, 2001, vol. 29, no. 7, e36, p. 1-7) and Harris et al. (US Patent 5,849,544; December 1998). Urdea teaches a method for nucleic acid detection and signal amplification to reduce background (Abstract).

With regard to claim 20, Urdea teaches a kit comprising a solid support selected from the group consisting of a solid support that comprises:

a) a capture probe and one or more target capture probes linked to the solid support at the 3' terminus directly or with spacers, one or more target capture extenders with sequences complementary to a sequence on a target capture probe and a target nucleic acid molecule, and a discrimination extender with an unblocked 3' terminus that and a sequence complementary to a sequence on a capture probe and a target nucleic acid molecule (Figure 10, and col. 13, line 44 to col. 15, line 49, where capture probes are linked to the solid support, capture extender probes are complementary to a target and on the capture probe);

b) a capture probe and one or more target capture probes linked to the solid support at the 5' terminus directly or with spacers, one or more target capture extenders with sequences

complementary to a sequence on a target capture probe and a target nucleic acid molecule, and a discrimination extender with an phosphorylated 5' terminus and a sequence complementary to a sequence on a capture probe and a target nucleic acid molecule;

c) a capture probe linked to the solid support at the 3' termini directly or with spacers, one or more target capture probes linked to the solid support at the 5' terminus directly or with spacers, one or more target capture extenders with sequences complementary to a sequence on a target capture probe and a target nucleic acid molecule, and a discrimination extender with an unblocked 3' terminus and a sequence complementary to a sequence on a capture probe and a target nucleic acid molecule (Figure 10, and col. 13, line 44 to col. 15, line 49, where capture probes are linked to the solid support, capture extender probes are complementary to a target and on the capture probe).

With regard to claim 22, Urdea teaches a solid support selected from the group consisting of: a) a solid support comprising a discrimination probe linked to the solid support at the 5' termini directly or with spacers, one or more target capture probes linked to the solid support at the 5' terminus directly or with spacers, wherein a sequence of a target probe is complementary to a sequence on a target nucleic acid molecule and a sequence on the discrimination probe is complementary to a sequence on the target nucleic acid molecule (Figure 10, and col. 13, line 44 to col. 15, line 49, where capture probes are linked to the solid support, capture extender probes are complementary to a target and on the capture probe);

b) a solid support comprising a discrimination probe linked to the solid support at the 3' termini directly or with spacers, one or more target capture probes and linked to the solid support at the 3' terminus directly or with spacers, wherein a sequence of a target probe is complementary to a

sequence on a target nucleic acid molecule and a sequence on the discrimination probe is complementary to a sequence on the target nucleic acid molecule (Figure 10, and col. 13, line 44 to col. 15, line 49, where capture probes are linked to the solid support, capture extender probes are complementary to a target and on the capture probe).

Regarding claims 20-23, Urdea does not teach that the discrimination probe is complementary to a single nucleotide polymorphism. Erdogan teaches a microarray comprising allele specific primer sequences attached in discrete location for detection of single nucleotide polymorphisms (Abstract).

With regard to claim 21 and 23, Erdogan teaches an embodiment of claim 20 or 22, wherein the solid support comprises more than one different discrimination probe, each different discrimination probe spatially separated at identifiable locations and different discrimination extenders having termini complementary to a single nucleotide polymorphism position of an allele of different genes (p. 2, materials and methods, col. 1, where the allele specific primers/probes were attached to a microarray in discrete locations; Figure 1, where match and mismatch primers/probes differ at their free 3' end variable base, which is discriminated by the enzyme).

Regarding claims 20-23, neither Urdea or Soderlund specifically teach the element wherein the capture probes have terminal nucleotides that are blocked and/or unphosphorylated. Harris teaches the use of capture probes where the 3' end is blocked through immobilization while the 5' end is rendered incapable of ligation or extension via lack of a phosphoryl group or through blockage with a variety of 5' substituents (col. 5, line 46 to col. 6, line 5). Harris also teaches the reverse set up, where the capture probe is immobilized at the 5' end and blocked at

the 3' end with suitable substituents to prevent reaction at the 3' end.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the technique of detection of variable nucleotides as taught by Soderlund into the method of Urdea to arrive at the claimed invention with a reasonable expectation for success. Both Urdea and Erdogan are focused on the inclusion of a solid support for the detection of nucleic acids. As taught by Urdea, "the invention is useful in conjunction with any number of assay formats wherein multiple hybridization steps are carried out to produce a detectable signal which correlates with the presence or quantity of a polynucleotide analyte" (col. 1, lines 39-43), while Erdogan teaches "oligonucleotide primers carrying polymorphic sites at their free 3' end were covalently bound to glass slides" (Abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the allele specific probes/primers of Erdogan for detection of polymorphic nucleotides into the solid support of Urdea to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the capture probes so that they were blocked or unphosphorylated to prevent extension of these primers during the extension or discrimination phase of the solid phase assay. As taught by Harris, "the capture probe is incapable of participation in the amplification stage. For example, it may be a capture oligodeoxynucleotide in which the 3' end is chemically bonded to the wall of the reaction vessel or bonded to solid phase material" (col. 5, lines 50-62). Therefore, it would have been obvious to employ methods known in the art to prevent primer extension or other reaction, including blocking terminal

nucleotides or dephosphorylating nucleotides at the 5' end. While the method of Erdogan teaches the extension of the allele specific primers for detection of the polymorphic site, the instant invention is directed to the solid support itself and not the use of the solid support in a method. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated the allele specific probes of Erdogan, with the blocked termini of Harris into the solid support of Urdea to arrive at the instant invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed November 5, 2008 have been fully considered but they are not persuasive.

Applicant argues "Urdea does not disclose or suggest a discrimination extender" and "does not disclose or suggest a discrimination extender with an unblocked 3' terminus and a sequence complementary to a sequence on a capture probe and a target nucleic acid molecule" (p. 2 of remarks). Applicant also argues "Erdogan relates to the detection of mitochondrial SNPs which utilizes oligonucleotide primers which bind to glass slides at their 5' ends" and "targets are amplified by PCR" (p. 2 of remarks). Applicant also states "Harris relates to methods of amplification and target detection techniques" and "Harris does not disclose or suggest a solid support which includes a target nucleic acid molecule which has not been amplified" (p. 3 of remarks).

Applicant concludes "Erdogan and Harris relate exclusively to amplifying target sequences. In contrast, Urdea relates to a hybridization assay for unamplified target". Applicant

also argues "as discussed in paragraph 8 of the amplification as filed, in cases where the target sequence includes SNPs, the prior art hybridization approach does not work because the differences in thermodynamic stabilities and melting temperatures are too small for effective discrimination" (p. 3 of remarks).

Regarding the combination with Erdogan, Applicant argues "it would not have been obvious to one skilled in the art to have applied the primers of Erdogan for detection of polymorphic nucleotides with a reasonable expectation for success, because the primers of Erdogan are utilized in amplification, not detection" and because one of ordinary skill "would not have been motivated to utilize an assay of Urdea to incorporate a discrimination extender complementary to a SNP because hybridization assays having more than one capture extender did not work for capturing target sequences containing SNPs" (p. 4 of remarks).

These arguments have been considered, but are not persuasive. First, it is noted that while Urdea does not explicitly teach the presence of discrimination extenders, Urdea teaches probes which meet the limitation of a discrimination extender, which are complementary to a target capture probe and to a target sequence. The instant specification does not explicitly define a discrimination extender as being distinct from the capture extender taught by Urdea and the instant specification. The additional limitations which would distinguish the discrimination extender from capture extender, with complementarity to a polymorphism with a blocked 3' end, are rendered obvious by the combined teaching of Erdogan and Harris.

Furthermore, contrary to applicant's arguments, the limitations of Erdogan and Harris are properly combinable with the disclosure of Urdea. Urdea teaches target sequences that are not

amplified and useful in methods of hybridization and detection. Next, it is noted that Erdogan is relied upon specifically for teaching the "discrimination extender" element of the claims which is complementary to a polymorphic site in the target. This probe/primer would render the discrimination extender of the instant claims obvious, regardless of the amplification state of the target used in Erdogan because in Erdogan and in the instant specification, the "discrimination" is not achieved only through hybridization and detection, the probe/primer is extended with an enzyme. Furthermore, while Erdogan teaches amplifying the target sequence, an asymmetrically amplified target comprising a single strand is used in the method of primer extension and SNP detection. Therefore, a single stranded target is used in Erdogan as in the instantly claimed method. Furthermore, is unclear how a single stranded target that has been previously amplified would be distinguished, within the kit, from a single strand of nucleic acid that was not amplified. Regarding Harris, the reference is not relied upon for the amplification of a target, but for the blocking of the probe and again, the amplification state of the target, does not teach away from a combination with Urdea.

Finally, while Applicant's arguments regarding the differences between a hybridization and detection assay of an unamplified target are noted, it is noted that the instantly claimed kits are specifically used in ligation or other enzymatic extension of the discrimination extender probe. Therefore, the teaching of paragraph 8 of the instant spec, " In case of targets that differ in their sequences by only one base (e.g. SNPs) this approach does not work for more than one capture extender, because the differences in thermodynamic stabilities and thus melting temperatures are too small for effective discrimination" is not relevant to the instant combination of references. In the combination of Urdea, Erdogan and Harris, the SNP is detected, not only

through a difference in melting temperature, but through specific extension of the probe/primer which is complementary to the polymorphic site.

For these reasons, the claims are rendered obvious and the rejections are maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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